

**NEW ZEALAND DATA SHEET
DOXORUBICIN EBEWE (DOXORUBICIN)**

1. PRODUCT NAME

Doxorubicin Ebewe concentrate for injection 2 mg/mL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active: Doxorubicin hydrochloride

Each vial of Doxorubicin Ebewe contains 10 mg, 20 mg, 50 mg and 200 mg of doxorubicin hydrochloride as a solution (2 mg/mL).

It is soluble in water and slightly soluble in methanol.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Doxorubicin hydrochloride solution for injection is red in colour.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

Doxorubicin has been used successfully to produce regression in neoplastic conditions, e.g. acute leukaemia, Wilms' tumour, neuroblastoma, soft tissue and bone sarcomas, breast carcinoma, lymphomas of both Hodgkin's and non-Hodgkin's type, bronchogenic (lung) carcinoma, thyroid carcinoma, hepatomas and ovarian carcinoma etc. The main antitumour activities are listed in Table 1.

Doxorubicin is also indicated in the primary management of nonmetastatic carcinoma of the bladder (Tis, T₁, T₂) by intravesical administration.

Table 1 Doxorubicin Antitumour Activity

	Tumour Type	Response Rate (%)	Median Duration (month)	First Line Chemotherapy
Established Activity	Breast	35	3-6	Yes
	Ovary	38	3-6	?
	Lung	30	3	?
	Sarcoma	30	4	Yes
	Wilms'	66	4	Yes
	Bladder	28	4-6	?
	Neuroblastoma	41	4	Yes
	Hodgkin's	36	4-6	?
	Non-Hodgkin's Lymphoma	40	4-6	Yes
	Acute Leukaemia	35	3	?
	Hepatoma	32	4-6	Yes
	Thyroid	30	6-10	Yes
Some Response	Stomach	30	2-4	?Yes
	Cervix	32	2-6	?
	Head & Neck	19	2-4	

	Tumour Type	Response Rate (%)	Median Duration (month)	First Line Chemotherapy
	Testicle	20	3-6	
	Myeloma	33	3	
	Endometrial	36	4-6	?Yes
Unresponsive	Colorectal Pancreas Renal Melanoma Brain			

4.2. DOSE AND METHOD OF ADMINISTRATION

Dosage

The recommended dosage schedule is 60 to 75 mg/m² body surface area, as a single intravenous injection administered at 21-day intervals. The lower dose should be given to patients with inadequate marrow reserves due to old age, prior therapy, or neoplastic marrow infiltration. An alternative dose schedule is 25 to 30 mg/m² on each of three successive days, repeated every three to four weeks. The adult dosage regimens may be suitable for paediatric cases. The recommended lifetime cumulative dose limit is 550 mg doxorubicin hydrochloride/m² body surface area. Doxorubicin has been administered as an intra-arterial infusion for one to three days at doses of 45 to 100 mg/m².

Doxorubicin has been used in combination with other approved chemotherapeutic agents. Though evidence is available that at least in some types of neoplastic disease combination chemotherapy is superior to single agents, the benefits and risks of such therapy have not yet been fully elucidated.

Method of administration

General Directions

The product is for single use in one patient only. Doxorubicin injection contains no antimicrobial agent. Discard any residue.

The use of a Pharmacy Bulk Pack should be restricted to suitably qualified pharmacists operating in suitably equipped hospital pharmacies or compounding centres.

Do not administer doxorubicin by intramuscular or subcutaneous injection (see Section 4.3 Contraindications).

Care in the administration of doxorubicin will reduce the chance of perivenous infiltration. It may also decrease the chance of local reactions, e.g. urticaria and erythematous streaking.

It is recommended that doxorubicin be slowly administered into the tubing of a freely running intravenous infusion of sodium chloride 0.9% injection or glucose 5% injection. The tubing should be attached to a butterfly needle inserted preferably into a large vein. The rate of administration is dependent on the size of the vein and the dosage. However, the dose should be administered in not less than three to five minutes.

Local erythematous streaking along the vein as well as facial flushing may be indicative of too rapid administration. A burning or stinging sensation may be indicative of perivenous infiltration and the infusion should be immediately terminated and restarted in another vein.

Intravesical administration

The following procedure is recommended.

The bladder should be catheterised and emptied.

Add doxorubicin 80 mg to normal saline (final volume of 100 mL) and instil via the catheter into the bladder.

The catheter should be removed and the patient instructed to lie on one side. At 15-minute intervals over a one-hour period, the patient should alternate to the opposite side.

The patient should be instructed not to urinate for one hour, after which the bladder should be emptied of solution.

The procedure should be repeated at monthly intervals.

Handling precautions

As with all antineoplastic agents, trained personnel should prepare Doxorubicin Injection. This should be performed in a designated area (preferably a cytotoxic laminar flow cabinet). Protective gown, mask, gloves and appropriate eye protection should be worn when handling doxorubicin. Where solution accidentally contacts skin or mucosa, the affected area should be immediately washed, thoroughly with soap and water. It is recommended that pregnant personnel not handle cytotoxic agents such as doxorubicin.

Luer-Lok fitting syringes are recommended. Large bore needles are recommended to minimise pressure and possible formation of aerosols. Aerosols may also be reduced by using a venting needle during preparation.

Dosage adjustment in:

- renal impairment

Doxorubicin and its metabolites are excreted in the urine to a minor degree and there are no clear indications that the pharmacokinetics or toxicity of doxorubicin are altered in patients with impaired renal function.

- hepatic impairment

Doxorubicin is metabolised by the liver and excreted in bile. Impairment of hepatic function results in slower excretion of the drug and consequently increased retention and accumulation in the plasma and tissues, resulting in enhanced clinical toxicity.

Doxorubicin dosage must be reduced if hepatic function is impaired according to serum bilirubin levels and bromsulphophthalein (BSP) retention, as follows. If the serum bilirubin level is 20 to 50 micromol/L and the BSP retention is 9 to 15%, the recommended dose is one-half the normal dose. If the serum bilirubin level is over 50 micromol/L and the BSP retention is over 15%, the recommended dose is one-quarter of the normal dose.

➤ Elderly

It is recommended that the total cumulative dose of doxorubicin for adults aged 70 years or older be restricted to 400 mg/m² body surface area.

➤ Children

Adult dosage regimens may be suitable for paediatric cases.

Periodic assessment of cardiac function is recommended for children who have been treated with doxorubicin, as they may be at particular risk of developing delayed cardiotoxicity (see Section 4.4 Special warnings and precautions for use).

4.3. CONTRAINDICATIONS

Marked myelosuppression or severe stomatitis induced by previous treatment with other antitumour agents or by radiotherapy.

Impaired cardiac function. Intravenous doxorubicin should not be administered to patients with severe arrhythmias, myocardial insufficiency or myocardial infarction (see Section 4.4 Special warnings and precautions for use).

Patients who have previously received the full cumulative dose of doxorubicin, daunorubicin or epirubicin, idarubicin and/or other anthracyclines and anthracenediones

Pregnancy and lactation (see Section 4.6 Fertility, pregnancy and lactation).

Marked hepatic impairment.

Generalised infection.

Patients with hypersensitivity to doxorubicin and/or other anthracyclines or anthracenediones, or to other ingredients in the preparation.

Intravesical use is contraindicated in the following.

Invasive tumours which have penetrated the bladder wall, urinary infections, inflammation of the bladder, haematuria, catheterisation of the bladder (e.g. due to massive intravesical tumours).

Doxorubicin should not be administered by intramuscular or subcutaneous injection, as administration by these routes will result in severe tissue necrosis.

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Experienced doctor

Doxorubicin should be administered only under the supervision of a doctor who is experienced in the use of cancer chemotherapeutic agents, and only when the potential benefits of doxorubicin therapy outweigh the possible risks. Appropriate facilities should be available for adequate management of complications should they arise.

Doxorubicin is not an antimicrobial agent.

Patients should recover from acute toxicities of prior cytotoxic treatment (such as stomatitis, neutropenia, thrombocytopenia, and generalised infections) before beginning treatment with doxorubicin.

Initial treatment with doxorubicin requires close observation of the patient and extensive laboratory monitoring.

It is strongly recommended therefore, that patients be hospitalised at least during the first phase of treatment. Blood count and liver function tests should be carried out prior to each doxorubicin treatment.

Doxorubicin should be handled with care. If either of the preparations comes in contact with the skin or mucosae, the appropriate areas should be washed thoroughly with soap and water.

Cardiac toxicity

Special attention must be given to the cardiac toxicity exhibited by doxorubicin. Although uncommon, acute left ventricular failure has occurred, particularly in patients who have received total dosage of the drug exceeding the currently recommended limit of 550 mg/m² body surface area. For this reason, cardiac function should be assessed before undergoing treatment with Doxorubicin and has to be carefully monitored throughout therapy to minimize the risk of incurring severe cardiac impairment.

For patients who have had mediastinal irradiation, concurrent high dose cyclophosphamide or hypertensive cardiomegaly, it is recommended that the cumulative total lifetime dose of doxorubicin (including related drugs, e.g. daunorubicin and epirubicin) be less than 400 mg/m² body surface area.

Congestive heart failure and/or cardiomyopathy usually develops within two months of termination of doxorubicin therapy, but may not occur until several months to years after discontinuation of doxorubicin therapy. Delayed cardiomyopathy is manifested by reduced left ventricular ejection fraction (LVEF) and/or signs and symptoms of congestive heart failure (CHF) such as dyspnea, pulmonary oedema, dependent oedema, cardiomegaly and hepatomegaly, oliguria, ascites, pleural effusion, and gallop rhythm. Subacute effects such as pericarditis/myocarditis have also been reported. Life-threatening CHF is the most severe form of anthracycline-induced cardiomyopathy and represents the cumulative dose-limiting toxicity of the drug. Delayed onset cardiomyopathy may be fatal in as many as 60% of the patients who develop it. It is more likely to occur in children or elderly patients, patients previously treated with radiotherapy to the chest, or those given relatively high single doses, infrequently. Delayed onset cardiomyopathy may appear in response to stressful situations (e.g. Surgery, pregnancy), exercise (e.g. weight lifting) or acute viral infection.

Cardiac failure is often not favourably affected by presently known medical or physical therapy for cardiac support. Early clinical diagnosis of drug induced heart failure appears to be essential for successful treatment with digitalis, diuretics, low salt diet and bed rest. Severe cardiac toxicity may occur precipitously without antecedent electrocardiographic (ECG) changes. Baseline ECG and periodic follow-up ECG during and immediately after active drug therapy are advisable precautions. Transient ECG changes, e.g. T wave flattening, ST depression and arrhythmias, are not considered indications for suspension of doxorubicin therapy. A persistent reduction in the voltage of the QRS wave is presently considered more specifically predictive for cardiac toxicity. If this occurs, the benefit of continued therapy must be carefully evaluated against the risk of producing irreversible cardiac damage.

Measurement of the left ventricular ejection fraction using echocardiography or multigated radionuclide angiography (MUGA) is more sensitive and specific than ECG testing for evaluating and monitoring cardiac function. Endomyocardial biopsy is considered to be the most definitive test for anthracycline induced cardiotoxicity but is invasive.

A decrease of the LVEF is the most predictive event related to chronic, cumulative dose-dependent cardiomyopathy. When a pre-treatment (baseline) assessment of LVEF is available, this parameter can be used as an indicator of cardiac function throughout therapy.

Cardiac function test methods should be employed in the following order: ECG testing left ventricular ejection fraction, endomyocardial biopsy. If testing indicates possible myocardial toxicity, the benefit of continued therapy must be carefully evaluated against the risk of producing irreversible cardiac damage.

Cardiac function should be routinely assessed before doxorubicin therapy is initiated, and monitored periodically during treatment, to reduce the risk of severe cardiac impairment developing. Since functional impairment may be masked by compensatory hypertrophy, patients with previous abnormal test results should continue to be considered at risk. Left ventricular function should be evaluated before each dose of doxorubicin in excess of a cumulative anthracycline dose of 450 mg/m².

Monitoring of cardiac function is particularly important in the presence of any additional risk factors, as cardiac toxicity may occur at lower cumulative doses in these people. Additional risk factors include a history of cardiovascular disease, impaired cardiac function, previous or concurrent therapy with cardiotoxic drugs (e.g. anthracyclines, anthracenediones, cyclophosphamide, 5-fluorouracil), previous mediastinal radiotherapy, extremes in age, liver disease, whole body hyperthermia and female gender (mainly in children). Irradiation of the left breast appears to be an important cardiotoxic risk factor.

Because anthracycline induced, cardiotoxicity may develop long after discontinuation of therapy with the drug, periodic monitoring of cardiac function, with evaluation of left ventricular ejection fraction, should be continued throughout the patient's lifetime.

Patients with a history of cardiovascular disease should only be treated with doxorubicin if the benefits outweigh the risks to the patient.

Children and adolescents are at an increased risk for developing delayed cardiotoxicity following doxorubicin administration. Females may be at greater risk than males. Follow-up cardiac evaluations are recommended periodically to monitor for this effect.

If any additional risk factor for cardiac toxicity is present, cardiac toxicity might occur at lower cumulative doses and the monitoring of cardiac function must be particularly strict. Risk factors for cardiac toxicity include a previous history of heart disease, prior or concomitant radiotherapy to the mediastinal/pericardial area, previous treatments with anthracyclines or anthracenediones, concomitant use of other cardioactive compounds (e.g. calcium channel blocking drugs) or concomitant use of other potentially cardiotoxic drugs (e.g. cyclophosphamide, 5-fluorouracil or trastuzumab).

Anthracyclines including doxorubicin should not be administered in combination with other cardiotoxic agents unless the patient's cardiac function is closely monitored. Patients receiving anthracyclines after stopping treatment with other cardiotoxic agents, especially those with long half-lives such as trastuzumab may also be at an increased risk of developing cardiotoxicity. The half-life of trastuzumab is approximately 28.5 days, however may be variable and may persist in the circulation for up to 7 months. Therefore, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab when possible. If anthracyclines are used before this time, careful monitoring of cardiac function is recommended.

Obese patients

Systemic doxorubicin clearance tends to be decreased in obese patients; such patients must be carefully monitored if they are being treated with the maximum recommended doses of doxorubicin.

Bone marrow depression

There is high incidence of bone marrow depression, primarily of leucocytes, requiring careful haematological monitoring. With the recommended dosage schedule, leucopenia is usually transient, reaching its nadir at 10 to 14 days after treatment, with recovery usually occurring by the 21st day. White blood cell counts as low as 1,000/mm³ are to be expected during treatment with appropriate doses of doxorubicin. Red blood cell and platelet levels should also be monitored, since they may also be depressed.

Haematological toxicity may require dose reduction or suspension or delay of doxorubicin therapy.

When using doxorubicin as part of chemotherapy regimens, which combine drugs of similar pharmacological effects (i.e. cytotoxicity) additive, toxicity is likely to occur. Such additive toxicity has to be taken into consideration especially with regard to bone marrow function.

Doxorubicin is a powerful but temporary immunosuppressant agent. Appropriate measures should be taken to prevent secondary infection. Persistent severe myelosuppression may result in superinfection or haemorrhage.

Immunosuppressant Effects/Increased Susceptibility to Infections

Administration of live or live attenuated vaccines in patients immunocompromised by chemotherapeutic agents including doxorubicin may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving doxorubicin. Killed or inactivated vaccines may be administered; however, the response to such vaccines may be diminished.

Doxorubicin is a powerful but temporary immunosuppressive agent. Appropriate measures should be taken to prevent secondary infection.

The risks and benefits should be considered before treating patients with an infection with doxorubicin, due to its immunosuppressive effects. Doxorubicin should only be administered with caution to patients with herpes zoster or with existing or recent chicken pox (including recent exposure), as there is a risk that severe generalised disease will develop.

Immunisation of patients being treated with doxorubicin should only be undertaken with extreme caution, after a careful review of the patient's haematological status, as doxorubicin may suppress normal defence mechanisms. Concurrent use of doxorubicin with live virus vaccines may potentiate the replication of the vaccine virus, increase adverse effects of the vaccine, and/or may decrease the patient's antibody response to the vaccine. Doxorubicin may also decrease the patient's antibody response to killed virus vaccines. The interval between discontinuation of medications that cause immunosuppression and restoration of the patient's ability to respond to the vaccine depends on many factors; estimates vary from three months to one year.

Patients with leukemia, which is in remission, should not receive live virus vaccines until at least three months after their last chemotherapy treatment.

People in close contact with a patient who is being treated with doxorubicin, especially family members, should postpone immunisation with oral polio vaccines.

Severe myelosuppression

Persistent severe myelosuppression may result in superinfection or haemorrhage.

Dental

The bone marrow depressant effects of doxorubicin may cause an increased incidence of microbial infection, delayed healing and gingival bleeding. Patients should be instructed in proper oral hygiene during treatment, including caution in the use of toothbrushes, dental floss and toothpicks. Dental work, whenever possible, should be completed prior to initiation of therapy, or deferred until blood counts have returned to normal.

Other

It has been reported that doxorubicin may enhance the severity of the toxicity of anticancer therapies, e.g. cyclophosphamide induced haemorrhagic cystitis, mucositis, cardiotoxicity and bone marrow depressant effects induced by radiotherapy and hepatotoxicity of 6-mercaptopurine. Radiation-induced toxicities (myocardium, mucosae, skin and liver) have also been reported.

As with other cytotoxic agents, thrombophlebitis and thromboembolic phenomena, including pulmonary embolism (in some cases fatal), have been coincidentally reported with the use of doxorubicin.

Extravasation

On intravenous administration of doxorubicin, a stinging or burning sensation signifies extravasation and, even if blood return from aspiration of the infusion needle is good, the injection or infusion should be immediately terminated and restarted in another vein. Extravasation is serious and may produce extensive local necrosis and ulceration.

General precautions

Initial treatment with doxorubicin requires close observation of the patient and extensive laboratory monitoring.

It is strongly recommended therefore that patients be hospitalised at least during the first phase of treatment. Blood count and liver and cardiac function tests should be carried out prior to and at regular intervals during each doxorubicin treatment.

Patients should be advised that doxorubicin can discolour the urine red for one to two days after administration. This red colouring is not indicative of haematuria.

Doxorubicin should be handled with care. If the solution comes in contact with the skin or mucosa, the area should be washed thoroughly with soap and water.

Routine use of doxorubicin as adjuvant therapy in any tumour category is not recommended. The activity of doxorubicin in combination with other drugs is affected not only by the nature of the drug itself, but also by the schedule of administration.

Doxorubicin and related compounds have been shown to have mutagenic and carcinogenic properties when tested in experimental models.

Secondary oral neoplasms

Very rare cases of secondary oral cancer have been reported in patients with long-term (more than one year) exposure to doxorubicin or those receiving a cumulative doxorubicin dose greater than 720 mg/m². Cases of secondary oral cancer were diagnosed both, during treatment with doxorubicin, and up to 6 years after the last dose. Patients should be examined at regular intervals for the presence of oral ulceration or any oral discomfort that may be indicative of secondary oral cancer.

Intravesical administration

Urine cytologies and blood counts should be monitored monthly, and cystoscopic examinations should be performed at regular intervals.

Tumor-Lysis Syndrome

Like other cytotoxic drugs, doxorubicin may induce hyperuricaemia secondary to rapid lysis of neoplastic cells (tumor-lysis syndrome). The clinician should monitor the patient's blood uric acid level, potassium, calcium phosphate and creatinine, and be prepared to use such supportive and pharmacologic measures as might be necessary to control this problem. Hydration, urine alkalinisation, and prophylaxis with allopurinol to prevent hyperuricaemia may minimise potential complications of tumor-lysis syndrome.

Instructions to be given to Patients

1. Patients should inform their physicians immediately if pain develops at the injection site.
2. Nausea and vomiting may be expected 3-6 hours after drug treatment, and may last for several hours.
3. Patients should be advised to expect a red colouration to the urine (not indicative of haematuria) for 1 to 2 days after each administration of doxorubicin.
4. Alopecia (hair loss) should be expected 1 to 2 weeks after the initiation of doxorubicin treatment. Hair loss may be complete but hair always returns after termination of treatment.

NB. Scalp tourniquets inflated to above systolic blood pressure and left in situ for 30 minutes over the time of doxorubicin treatment reduces the probability of alopecia.

5. Anorexia may be expected for 24 hours following each treatment and occasionally may persist for several days.
6. Hyperpigmentation, usually in the hands, nails and buccal mucosa may develop in patients receiving doxorubicin. Patients should be advised that this condition does not usually improve after termination of treatment.
7. Infertility in both sexes is usual in patients receiving doxorubicin. Amenorrhoea is frequent and in premenopausal women, regular menstruation usually returns a few months after termination of doxorubicin therapy. This is often accompanied by normal fertility.

Male patients should be advised that oligospermia or azospermia may be permanent. There is a possibility that fertility may return several years after ceasing therapy. Men undergoing doxorubicin therapy should be advised to use effective contraceptive measures.

8. Patients should be instructed to inform their physicians of any prior abnormal heart or liver conditions, as this information is vital to the formulation of appropriate dosage regimes.

Use in hepatic impairment

The toxicity of recommended doses of doxorubicin is enhanced by hepatic impairment. It is recommended that an evaluation of hepatic function be carried out prior to individual dosing, using conventional clinical laboratory tests, e.g. AST, ALT, alkaline phosphatase, bilirubin and bromsulphophthalein (BSP) retention. If required, dosage schedules should be reduced accordingly. (See Section 4.2 Dose and method of administration).

Changes in hepatic function induced by concomitant therapies, either given to achieve optimal antitumour efficacy or given for the pharmacological management of concomitant diseases, may affect doxorubicin metabolism, pharmacokinetics, therapeutic efficacy or toxicity.

Use in the elderly

Although appropriate studies with doxorubicin have not been performed in this population, cardiac toxicity may be more frequent in patients greater than or equal to 70 years of age. Caution should also be used in patients who have inadequate bone marrow reserves due to old age.

Paediatric use

Doxorubicin induced cardiomyopathy impairs myocardial growth as children mature, so that paediatric patients may be at particular risk of developing delayed cardiotoxicity and, possibly, subsequent congestive heart failure during early adulthood. Periodic follow-up is therefore recommended for children who have been treated with doxorubicin.

Effects on laboratory tests

No data available.

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Doxorubicin may potentiate the toxicity of other anticancer therapies.

Doxorubicin may exacerbate cyclophosphamide induced haemorrhagic cystitis and enhance the hepatotoxicity of 6-mercaptopurine (see Section 4.4 Special warnings and precautions for use – Enhanced toxicity).

Concurrent treatment with cyclophosphamide, dactinomycin or mitomycin may sensitise the heart to the cardiotoxic effects of doxorubicin. The cumulative dose of doxorubicin should be reduced in patients who have received other cardiotoxic drugs, including cyclophosphamide, mitoxantrone, idarubicin, daunorubicin or epirubicin.

A high incidence of congestive heart failure has been reported in patients who have received doxorubicin in association with paclitaxel.

Propranolol may increase the cardiotoxicity of doxorubicin as both drugs have been shown to inhibit cardiac mitochondrial coenzyme Q10.

Concurrent administration of calcium channel blockers with doxorubicin may increase the risk of cardiotoxicity.

Doxorubicin may raise the concentration of blood uric acid, secondary to rapid lysis of neoplastic cells; dosage adjustment of antigout agents (e.g. allopurinol, colchicine, probenecid, sulfapyrazone) may be necessary to control hyperuricaemia. Serum uric acid concentrations should be monitored. Adequate oral hydration may prevent development of uric acid

nephropathy. Alkalinisation of the urine may be necessary in some cases where serum uric acid concentrations are elevated.

The leucopenic, thrombocytopenic and bone marrow depressant effects of doxorubicin may be increased with concurrent or recent therapy with other drugs causing these effects. Symptoms may include severe dermatitis and/or mucositis. Dosage reduction may be required if doxorubicin is used concurrently or consecutively with other bone marrow depressants, including radiation therapy.

Doxorubicin may decrease the patient's antibody response to vaccines and/or may increase adverse effects of a live virus vaccine due to immunosuppression. This effect may persist from three months to one year (see Section 4.4 Special warnings and precautions for use).

Hepatotoxic medications (e.g. high dose methotrexate, streptozocin) may impair hepatic function and therefore increase the toxicity of subsequently administered doxorubicin.

Phenobarbitone induces liver enzymes; therefore, concurrent administration may increase the elimination of doxorubicin. Doxorubicin may decrease serum phenytoin concentrations.

Hypersensitivity reactions to doxorubicin have been reported following recent exposure to clindamycin. The possibility of cross sensitivity between anthracyclines and clindamycin should be considered. Apparent cross sensitivity to lincomycin has also been reported.

Severe neurotoxicity, presenting as seizures and/or coma, has occurred following concurrent administration of doxorubicin and cyclosporin.

Concurrent administration of doxorubicin and cytarabine may result in colitis and necrosis (see Section 4.8 Adverse effects).

Sorafenib: Both increases (21% - 47%) and no change in the AUC of doxorubicin were observed with concomitant treatment with sorafenib 400 mg twice daily. The clinical significance of these findings is unknown.

The addition of cyclosporine to doxorubicin may result in increases in area under the concentration-time curve (AUC) for both doxorubicin and doxorubicinol, possibly due to a decrease in clearance of the parent drug and a decrease in metabolism of doxorubicinol. Literature reports suggest that adding cyclosporine to doxorubicin results in more profound and prolonged hematologic toxicity than that observed with doxorubicin alone. Coma and seizures have also been described with concomitant administration of cyclosporine and doxorubicin.

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Doxorubicin may cause infertility during the time of drug administration. In women, doxorubicin may cause amenorrhea. Although ovulation and menstruation appear to return after termination of therapy, premature menopause can occur.

Doxorubicin was toxic to male reproductive organs in animal studies, producing testicular atrophy, diffuse degeneration of the seminiferous tubules, and hypospermia.

Doxorubicin may cause infertility during the time of drug administration in both sexes. In women, ovulation and menstruation appear to return a few months after termination of therapy. This is often accompanied by normal fertility. Oligospermia or azoospermia in male patients

may be permanent, although there is a possibility that fertility may return more than five years after ceasing therapy.

Use in pregnancy

Category D

Doxorubicin should not be administered to pregnant women (see Section 4.3 Contraindications). Women of childbearing potential should be advised to avoid becoming pregnant while they, or their partner, are being treated with doxorubicin, and for six months following completion of doxorubicin therapy.

Doxorubicin has been reported to be embryotoxic and teratogenic in rats, and embryotoxic and abortifacient in rabbits. Studies with rabbits and rats have revealed a decreased weight gain, and a higher incidence of resorbed fetuses. Doxorubicin has been found in fetal tissue (liver, kidney and lungs) at concentrations several times that in maternal plasma, indicating that doxorubicin crosses the placenta. Dose related mutagenicity (indicated by severe chromosomal aberrations) has been reported *in vitro*. In view of this activity, the use of doxorubicin in pregnant women is not recommended.

Use in lactation

Doxorubicin is distributed into milk, but limited data suggest that the amount of active drug estimated to be ingested by a breastfed infant would be small. However, because of the potential for serious adverse reactions to doxorubicin in breastfed infants, breastfeeding is not recommended.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Not relevant.

4.8. UNDESIRABLE EFFECTS

More common reactions

Cardiovascular. Cardiotoxicity (usually appears one to six months after initiation of therapy), i.e. cardiomyopathy, congestive heart failure. Acute life-threatening arrhythmias have been reported during or within a few hours of administration.

Dermatological. Extravasation, skin necrosis, cellulitis, vesication, phlebitis, reversible complete alopecia, thrombophlebitis, lymphangitis, painful induration, erythematous streaking along the vein proximal to the site of injection, phlebosclerosis.

Gastrointestinal. Nausea and vomiting, mucositis (stomatitis and oesophagitis), diarrhoea, abdominal pain.

General. Dehydration, facial flushing (if an injection has been given too rapidly).

Haematological. Myelosuppression, leucopenia.

Liver. Changes in transaminase levels.

Other. Red discolouration of urine (see Section 4.4 Special warnings and precautions for use). ***Less common reactions***

Dermatological. Urticarial rash, hyperpigmentation of nail beds, soles and dermal creases (primarily in children in a few cases), recall of skin reaction due to prior radiotherapy,

producing erythema with vesiculation, non-pitting oedema, severe pain, moist desquamation and palmar plantar erythrodysesthesia.

General. Chills and fever, generalised muscle weakness, anorexia, allergic reactions, anaphylaxis.

Haematological. Thrombocytopenia, anaemia, febrile neutropenia, septicemia, and death. The occurrence of secondary acute myeloid leukaemia with or without a preleukaemic phase has been reported rarely in patients concurrently treated with DNA damaging antineoplastic agents. Such cases could have a short (one to three year) latency period.

Nervous system. Drowsiness.

Ocular. Conjunctivitis, lacrimation.

Renal. Renal damage, hyperuricaemia, uric acid nephropathy.

Cardiovascular. Pericardial effusions, thromboembolism.

Gastrointestinal. Bleeding, ulceration, and necrosis of the colonic mucosa, which may be associated with severe and sometimes fatal infections, have occurred in patients with acute myelogenous leukaemia treated concurrently with doxorubicin and cytarabine.

Reproductive. Amenorrhoea, azoospermia (see Sections 5.3 Preclinical safety data – Genotoxicity, Carcinogenicity and 4.6 Fertility, pregnancy and lactation – Effects on fertility).

Other. Hot flushes, malaise/asthenia, shock.

Post-Marketing Experience

Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Very rare: Secondary oral neoplasms (See Section 4.4 Special warnings and precautions for use)

Severe or life-threatening reactions

Myelosuppression. This accompanies effective doxorubicin treatment in almost 100% of patients. Leucopenia is the predominant effect with thrombocytopenia and anaemia occurring less frequently.

Myelosuppression is more common in patients who have had extensive radiotherapy, bone infiltration by the tumour, impaired hepatic function (when appropriate dosage reduction has not been adopted; see Section 4.2 Dose and method of administration – Dosage adjustment in, hepatic impairment) and simultaneous treatment with other myelosuppression agents. The nadir (time from treatment to peripheral blood evidence of maximal myelosuppression) of leucopenia and thrombocytopenia is 10 to 15 days after treatment, and counts return to normal before day 21.

Haematological. The occurrence of secondary acute myeloid leukaemia with or without a preleukaemic phase has been reported in patients concurrently treated with doxorubicin in association with DNA-damaging antineoplastic agents. Secondary leukemia is more common when such drugs are given in combination with DNA-damaging antineoplastic agents, in combination with radiotherapy, when patients have been heavily pretreated with cytotoxic drugs, or when doses of the anthracyclines have been escalated. This has been noted in the adjuvant and neoadjuvant setting. Such cases may have a short (1-3 year) latency period.

Mucositis. This phenomenon is a frequent and painful complication of doxorubicin treatment but is less common than myelosuppression. Mucositis most commonly develops five to ten days after treatment, and typically begins as a burning sensation in the mouth and pharynx. The mucositis may involve the vagina, rectum and oesophagus, and may progress to ulceration with risk of secondary infection. The mucositis usually subsides in ten days. Retrospective comparison of the incidence of mucositis suggests that it is less frequent as the intervals between doses increase. Mucositis may be severe in patients who have had previous irradiation to the mucosae.

Cardiotoxicity. The cardiac abnormalities caused by doxorubicin treatment can be separated into two categories: ECG alterations and congestive heart failure.

ECG changes following doxorubicin treatment occur in about 10% of patients at all dose levels of doxorubicin, are usually reversible and do not appear to be related to the subsequent development of congestive cardiac failure. The total (cumulative) dose levels of doxorubicin do correlate with the incidence of drug induced congestive cardiac failure (cardiomyopathy). Limitation of the total dose of doxorubicin to 550 or 400 mg/m² (see Section 4.4 Special warnings and precautions for use) reduces the risk of drug induced cardiomyopathy. Severe cardiotoxicity may occur months or even years after administration of doxorubicin. Delayed onset cardiotoxicity is frequently fatal (see Section 4.4 Special warnings and precautions for use).

At the cellular level, doxorubicin induced cardiotoxicity is due to myocyte damage. Furthermore, as a consequence of the inhibition of cellular proliferation not only of neoplastic cells but also of normal cells, cardiac muscle cells are unable to regenerate.

Microscopic examination of endocardial biopsies shows two major types of myocyte damage: cells totally or partially devoid of myofibrillar content, even though the nucleus and mitochondria are intact; and vacuolar degeneration.

Damage to the myocardial muscle occurs with very little inflammatory reaction: muscle fibres appear to fade away. The clinical spectrum of doxorubicin toxicity ranges from subtle changes in ventricular function that can be detected only by sophisticated studies, to gross congestive cardiomyopathy with symptoms and signs of advanced congestive heart failure.

The following measures may identify patients with early doxorubicin cardiomyopathy: progressive flattening or inversion of the T waves (mainly in the left praecordial leads), low QRS voltage, prolonged systolic time interval, reduced ejection fraction (as determined by echocardiography or cardiac pool scanning) or cardiac biopsy showing characteristic electronmicroscopic changes. Doxorubicin cardiomyopathy is frequently fatal. If diagnosed early, management with digoxin, diuretics and bed rest may control heart failure.

Animal studies have indicated a possible relationship between the inhibition by doxorubicin of the mitochondrial biosynthesis of coenzyme Q10 and doxorubicin induced cardiotoxicity. Other studies have suggested that vitamin E and other free radical acceptors may prevent doxorubicin toxicity.

Intravesical use. Systemic toxicity is not a common problem, however adverse effects have been noted at doses exceeding that recommended (see Section 4.2 Dose and method of administration).

Local reactions observed include chemical cystitis, contraction of the bladder, haematuria, painful micturition, frequency and urgency. These disturbances are transient. Special attention

is required for catheterisation problems (e.g., urethral obstruction due to massive intravesical tumours.).

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9. OVERDOSE

The symptoms of overdosage are likely to be an extension of doxorubicin's pharmacological action. Possible symptoms of toxicity are those listed under Adverse Reactions. Some toxicity may be delayed (e.g. Microcositis) or life threatening (e.g. Myelosuppression and cardiotoxicity).

Treatment

Symptomatic supportive measures should be instituted. Particular attention should be given to prevention and treatment of possible severe haemorrhages or infections secondary to severe, persistent bone marrow depression.

Acute animal toxicity

The acute toxicity of doxorubicin in Swiss mice varies greatly according to the route of administration. The LD₅₀ corresponds to 8.5 mg/kg by the intraperitoneal route, 21.1 mg/kg by the intravenous route, and is greater than 750 mg/kg by the oral route.

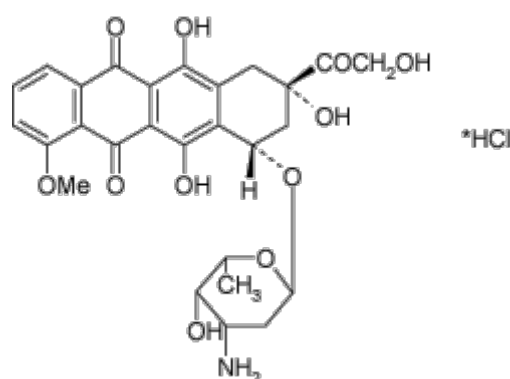
For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Doxorubicin hydrochloride: Molecular formula, C₂₇H₂₉NO₁₁.HCl. MW, 580.0 and CAS number, 25316-40-9.

Doxorubicin hydrochloride is a cytotoxic anthracycline antibiotic isolated from cultures of *Streptomyces peucetius* varians *caesius*. The chemical structure of doxorubicin consists of a tetracyclic ring with the sugar daunosamine attached by a glycosidic linkage. Structurally, doxorubicin is related to daunomycin (daunorubicin) and differs only in hydroxyl group substitution (instead of hydrogen) at the alkyl side chain at position '9' of the 'A' ring. It is supplied in solution form containing sodium chloride.



Mechanism of action

Though not completely elucidated, the mechanism of action of doxorubicin is related to its ability to bind to DNA and inhibit nucleic acid synthesis. Cell culture studies have demonstrated rapid cell penetration and perinucleolar chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, mutagenesis and chromosomal aberrations.

Doxorubicin has immunosuppressive effects. It inhibits the titre of haemolytic and haemagglutinating antibodies in mice immunised with sheep red blood cells. Similar evidence in humans indicates that doxorubicin is a powerful but temporary immunosuppressant agent. Doxorubicin is a cell cycle, phase nonspecific cytotoxic drug.

The toxic effects of doxorubicin on the bone marrow appear to be related to its action on proliferating myeloid cells. The cardiotoxicity of doxorubicin is probably mediated by different mechanisms. Although in animal systems, doxorubicin does inhibit DNA synthesis in cardiac muscle, it is probable that cardiotoxicity is not directly related to inhibition of cardiac muscle replication. There are some data that suggest that it is due to the generation of free radicals, which damage cardiac muscle in some uncertain way. These data also suggest that concurrent administration of vitamin E and other free radical acceptors may prevent cardiotoxicity in experimental animal systems without impairing antitumour efficacy. These studies need confirmation but they do suggest that it may be possible to divorce the antitumour effects of the drug from its cumulative cardiotoxic effects.

The specificity of doxorubicin toxicity appears to be related primarily to proliferative activity of normal tissue. Thus, the bone marrow, gastrointestinal tract and gonads are the main normal tissues damaged.

Clinical trials

No data available.

5.2. PHARMACOKINETIC PROPERTIES

Absorption

Doxorubicin is not suitable for oral administration as less than 5% of the drug is absorbed.

Distribution

Pharmacokinetic studies show the intravenous administration of normal or radiolabelled doxorubicin for injection is followed by rapid plasma clearance and significant tissue binding. No information on plasma protein binding of doxorubicin is available.

Metabolism

The metabolism and disposition of doxorubicin is still to be defined. The drug is metabolised predominantly by the liver to doxorubicinol and several aglycone metabolites. It should be noted that several of the metabolites are cytotoxic. However, it is not certain whether any are more cytotoxic than the parent compound. High levels of metabolites appear rapidly in plasma and undergo a distribution phase with a measurable short initial half-life. Metabolism may be impaired in patients with abnormal hepatic function.

Excretion

The disappearance of doxorubicin and its metabolites from the plasma follows a triphasic pharmacokinetic pattern with a mean half-life of the first phase of 12 minutes, of the second phase of 3.3 hours and of the prolonged third phase of 29.6 hours.

Urinary excretion of doxorubicin hydrochloride and its metabolites is prolonged and accounts for only 5% of the drug excreted during the first five days. Approximately 50% of an administered dose is excreted in bile, and an additional 30% is excreted in bile as conjugates.

Impairment of hepatic function results in slower excretion and, consequently, increased retention and accumulation in plasma and tissues. Doxorubicin does not cross the blood-brain barrier.

5.3. PRECLINICAL SAFETY DATA

Genotoxicity

Doxorubicin was genotoxic in a battery of *in vitro* or *in vivo* tests. An increase in the incidence of mammary tumours was reported in rats, and a trend for delay or arrest of follicular maturation was seen in female dogs.

Carcinogenicity

Doxorubicin and related compounds have been shown to have mutagenic and carcinogenic properties when tested in experimental models.

Doxorubicin is mutagenic and can induce chromosomal damage in human spermatozoa. Oligospermia or azoospermia may be permanent; however, sperm counts have been reported to return to normospermic levels in some instances. This may occur several years after the end of therapy. Men undergoing doxorubicin treatment should use effective contraceptive measures.

Secondary malignancies are potential delayed effects of many antineoplastic agents, although it is not clear whether the effect is related to their mutagenic or immunosuppressive action. Doxorubicin is carcinogenic in animals and is potentially carcinogenic in humans.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Sodium chloride, dilute hydrochloric acid and water for injections

6.2. INCOMPATIBILITIES

Doxorubicin should not be mixed with heparin, dexamethasone, fluorouracil, hydrocortisone sodium succinate, aminophylline, diazepam, frusemide or cephalothin, since it has been reported that these drugs are incompatible to the extent that a precipitate may form. Doxorubicin solution may darken in colour from red to purple if mixed with fluorouracil or aminophylline. Doxorubicin is reported to be incompatible with allopurinol, cefepime and ganciclovir.

Until specific compatibility data are available, it is not recommended that doxorubicin be mixed with other drugs.

Contact with alkaline solutions should be avoided since this can lead to hydrolysis of doxorubicin.

6.3. SHELF LIFE

24 months from date of manufacture.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C. Refrigerate. Do not freeze. Protect from light.

Storage of the medicinal product at refrigerated conditions can result in the formation of a gelled product. This gelled product will return to a slightly viscous to mobile solution after 2 to a maximum of 4 hours equilibration at controlled room temperature (15°C to 25°C).

6.5. NATURE AND CONTENTS OF CONTAINER

10 mg in 5 mL: glass vials; 1's

50 mg in 25 mL: glass vials; 1's

100 mg/50 mL: glass vial (pharmacy bulk pack, for hospital use only) vial; 1's

200 mg/100 mL: glass vial (pharmacy bulk pack, for hospital use only) vials; 1's

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

Spills and disposal

If spill occurs, restrict access to the affected area. Wear two pairs of latex rubber gloves, a suitable mask, a protective gown and safety glasses. Limit the spread of the spill by covering with a suitable material such as absorbent towels or adsorbent granules. Spills may also be treated with 5% sodium hypochlorite. Collect the absorbent/ adsorbent and other debris from the spill and place in a leakproof plastic container and label accordingly. Cytotoxic waste should be regarded as toxic and hazardous and clearly labelled 'Cytotoxic waste for incineration at 1100°C. Waste material should be incinerated at 1100°C for at least one second. Clean the remaining spill area with copious amounts of water.

Items used to prepare Doxorubicin Injection, or articles associated with body waste should be disposed of by placing in a double sealed polythene bag and incinerated at 1100°C.

Any unused medicine or waste material should be disposed of by taking to your local pharmacy.

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Sandoz New Zealand Limited
12 Madden Street
Auckland 1010
New Zealand

Telephone: 0800 726 369

9. DATE OF FIRST APPROVAL

26/01/2006

10. DATE OF REVISION OF THE TEXT

20/03/2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Change in sponsor details